

# **Document made available under the Patent Cooperation Treaty (PCT)**

International application number: PCT/GB05/000800

International filing date: 04 March 2005 (04.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB  
Number: 0419718.2  
Filing date: 06 September 2004 (06.09.2004)

Date of receipt at the International Bureau: 02 May 2005 (02.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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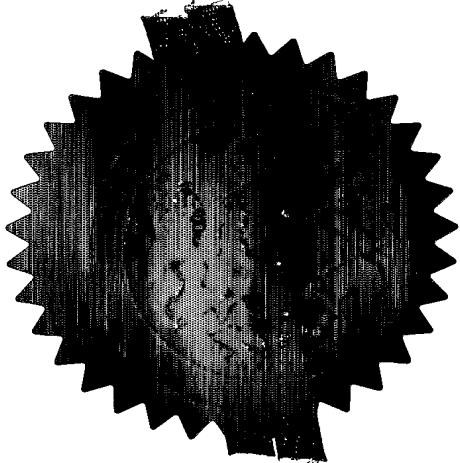
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1/77

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47627.GB04/NT

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0419718.2

06SEP04 E923860-1 D01631  
P01/7700 0.00-0419718.2 ACCOUNT CHA

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)

Cambridge Biotechnology Limited  
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Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of incorporation

820876/002

United Kingdom

4. Title of the invention

Therapeutic Compounds

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose  
16 Theobalds Road  
LONDON  
WC1X 8PL

Patents ADP number (*if you know it*)

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Dr N Thornton  
01223 360 350**Warning**

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47627.GB04

### Therapeutic Compounds

This invention relates to compounds that are adenosine receptor agonists, and to their use as therapeutic compounds, in particular as analgesic or anti-inflammatory compounds, and to methods of preventing, treating, or ameliorating pain or inflammation using these compounds.

Adenosine is a ubiquitous local hormone/neurotransmitter that acts on four known receptors, the adenosine A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> receptors. Adenosine generally serves to balance the supply and demand of energy in tissues. For example, in the heart released adenosine slows the heart by an A<sub>1</sub> receptor mediated action in the nodes and atria (Belardinelli, L & Isenberg, G Am. J. Physiol. 224, H734-H737), while simultaneously dilating the coronary artery to increase energy (i.e. glucose, fat and oxygen) supply (Knabb et al., Circ. Res. (1983) 53, 33-41). Similarly, during inflammation adenosine serves to inhibit inflammatory activity, while in conditions of excessive nerve activity (e.g. epilepsy) adenosine inhibits nerve firing (Klitgaard et al., Eur J. Pharmacol. (1993) 242, 221-228). This system, or a variant on it, is present in all tissues.

Adenosine itself can be used to diagnose and treat supraventricular tachycardia. Adenosine A<sub>1</sub> receptor agonists are known to act as powerful analgesics (Sawynok, J. Eur J Pharmacol. (1998) 347, 1-11). Adenosine A<sub>2A</sub> receptor agonists are known to act as anti-inflammatory agents (for example, from US 5,877,180 and WO 99/34804). In experimental animals, A<sub>2A</sub> receptor agonists have been shown to be effective against a wide variety of conditions including sepsis, arthritis, and ischaemia/reperfusion injury arising from renal, coronary or cerebral artery occlusion. The common factor in these conditions is a reduction in the inflammatory response caused by the inhibitory effect of this receptor on most, if not all, inflammatory cells.

However, the ubiquitous distribution of adenosine receptors means that administration of adenosine receptor agonists causes adverse side effects. This has generally precluded the development of adenosine-based therapies. Selective A<sub>1</sub> receptor agonists cause bradycardia. A<sub>2A</sub> receptor agonists cause widespread vasodilation

with consequent hypotension and tachycardia. The first selective A2A receptor agonist (2-[4-(2-carboxyethyl)phenylethylamino]-5'-N-ethylcarboxamidoadenosine, or CGS21680), was tested in a Phase 2A clinical trial as a potential anti-hypertensive. However, administration caused a large fall in blood pressure and consequent increase in cardiac output. FR 2162128 discloses that adenosine derivatives (including 2-alkoxy adenosine derivatives comprising a lower alkyl group of not less than two carbon atoms) have hypotensive and coronary vasodilatory activity.

Spongosine was first isolated from the tropical marine sponge, *Cryptotethia crypta* in 1945 (Bergmann and Feeney, J. Org. Chem. (1951) 16, 981, Ibid (1956) 21, 226), and was the first methoxypurine found in nature. It is also known as 2-methoxyadenosine, or 9H-purin-6-amine, 9-a-D-arabinofuranosyl-2-methoxy. The first biological activities of spongosine were described by Bartlett *et al.* (J. Med. Chem. (1981) 24, 947-954). Spongosine (and other compounds) was tested for its skeletal muscle-relaxant, hypothermic, cardiovascular and anti-inflammatory effects in rodents following oral administration (anti-inflammatory activity was assessed by inhibition of carageenan-induced oedema in a rat paw). Spongosine caused 25% inhibition of carageenan-induced inflammation in rats at 20 mg/kg po. However, reductions in mean blood pressure (41%), and in heart rate (25%) were also observed after administration of this compound at this dose.

The affinity of spongosine for the rat adenosine A1 and A2A receptors has been determined. The Kd values obtained (in the rat) were 340nM for the A1 receptor and 1.4 $\mu$ M for the A2A receptor, while the EC50 value for stimulation of the rat A2A receptor was shown to be 3 $\mu$ M (Daly *et al.*, Pharmacol. (1993) 46, 91-100). In the guinea pig, the efficacy of spongosine was tested in the isolated heart preparation and the EC50 values obtained were 10  $\mu$ M and 0.7  $\mu$ M for the adenosine A1 and A2A receptors, respectively (Ueeda *et al* J Med Chem (1991) 34, 1334-1339). Because of the low potency and poor receptor selectivity of this compound it was largely ignored in favour of more potent and receptor selective adenosine receptor agonists.

Pain has two components, each involving activation of sensory neurons. The first component is the early or immediate phase when a sensory neuron is stimulated, for

instance as the result of heat or pressure on the skin. The second component is the consequence of an increased sensitivity of the sensory mechanisms innervating tissue which has been previously damaged. This second component is referred to as hyperalgesia, and is involved in all forms of chronic pain arising from tissue damage, but not in the early or immediate phase of pain perception.

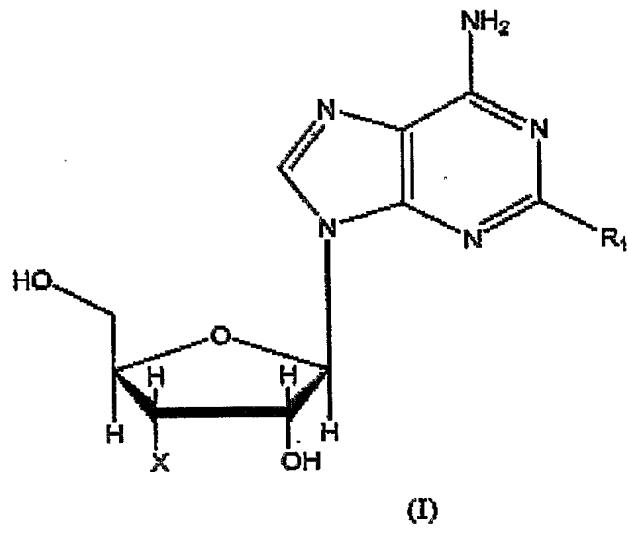
Thus, hyperalgesia is a condition of heightened pain perception caused by tissue damage. This condition is a natural response of the nervous system apparently designed to encourage protection of the damaged tissue by an injured individual, to give time for tissue repair to occur. There are two known underlying causes of this condition, an increase in sensory neuron activity, and a change in neuronal processing of nociceptive information which occurs in the spinal cord. Hyperalgesia can be debilitating in conditions of chronic inflammation (e.g. rheumatoid arthritis), and when sensory nerve damage has occurred (i.e. neuropathic pain).

Two major classes of analgesics are known: (i) non steroidal anti-inflammatory drugs (NSAIDs) and the related COX-2 inhibitors; and (ii) opiates based on morphine. Analgesics of both classes are effective in controlling normal, immediate or nociceptive pain. However, they are less effective against some types of hyperalgesic pain, such as neuropathic pain. Many medical practitioners are reluctant to prescribe opiates at the high doses required to affect neuropathic pain because of the side effects caused by administration of these compounds (such as restlessness, nausea, and vomiting), and the possibility that patients may become addicted to them. NSAIDs are much less potent than opiates, so even higher doses of these compounds are required. However, this is undesirable because these compounds cause irritation of the gastrointestinal tract.

There is, therefore, a need to provide adenosine receptor agonists that can be administered with minimal side effects. There is also a need to provide analgesics, particularly anti-hyperalgesics, which are sufficiently potent to control pain perception in neuropathic and other hyperalgesic syndromes, and which do not have serious side effects or cause patients to become addicted to them.

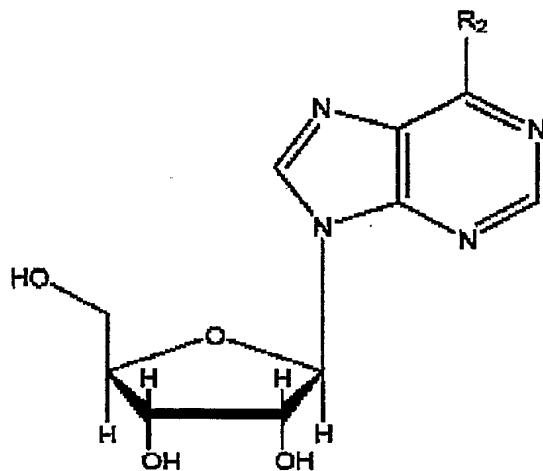
It has surprisingly been found that spongiosine is an effective analgesic at doses as much as one hundred times lower than would be expected to be required based on the known affinity of this compound for adenosine receptors. At these doses, spongiosine does not cause the significant side effects associated with higher doses of this compound, or other adenosine receptor agonists. The activity of spongiosine as an analgesic is the subject of International patent application no. PCT/GB03/05379, and the activity of compounds related to spongiosine as analgesics is the subject of International patent application no. PCT/GB04/00935 (unpublished at the filing date of the present application). Use of spongiosine and related compounds to treat inflammation and other disorders is the subject of International patent application no. PCT/GB04/000952 (unpublished at the filing date of the present application).

According to the invention there are provided adenosine receptor agonists of the following formulae:

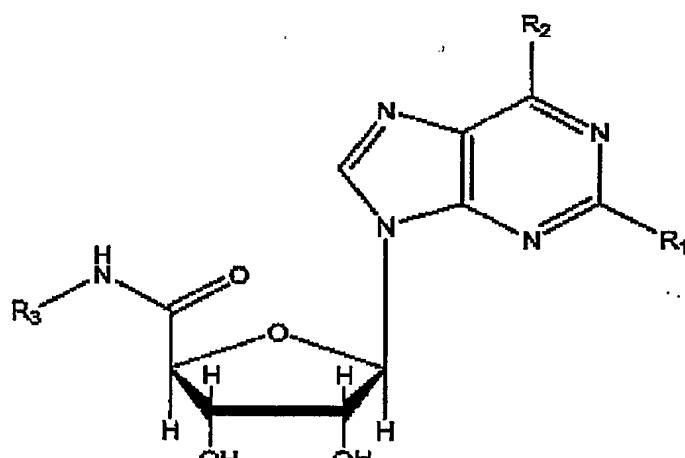


wherein:

when  $X = OH$ ,  $R_1$  is  $C_1$  or  $C_4-C_6$  alkoxy (preferably  $C_5-C_6$  alkoxy), phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy,  $C_1$ ,  $C_2$ ,  $C_5$ , or  $C_6$  alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isobutylamino), a  $C_2$  sulfone group, a  $C_7$  alkyl group, or  $OCH_2CH_2OH$ ; or  
when  $X = H$ ,  $R_1$  is *n*-hexyloxy;



wherein  $R_2$  is  $NMe_2$ ,  $N$ -(2-isopentenyl), piperazinyl, ( $N$ -Me,  $N$ -benzyl) or ( $N$ -Me,  $N$ -(2-methoxyethyl));



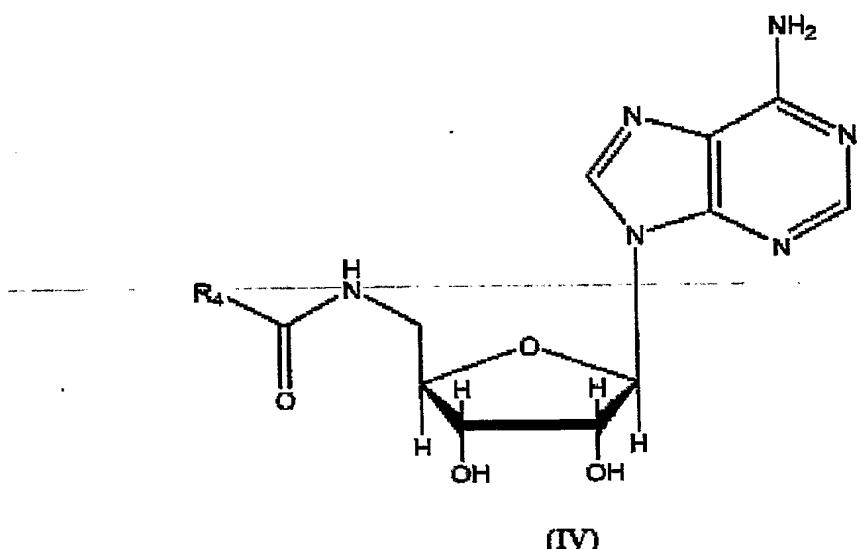
(III)

wherein:

when  $R_1 = H$ ,  $R_3$  is an isopropyl group, and  $R_2$  is either  $NH_2$  or a methylamino group ( $NHMe$ ); or

when  $R_1 = H$ ,  $R_3$  is  $H$ , and  $R_2$  is  $NH_2$ ; or

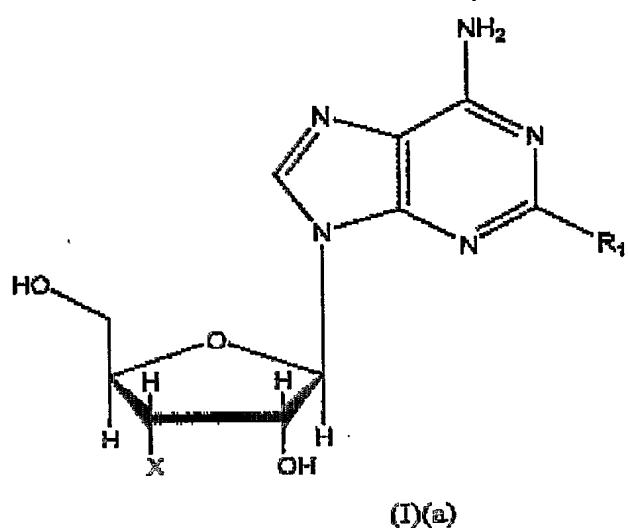
when  $R_1$  is  $OMe$ ,  $R_3$  is  $Ph$ , and  $R_2$  is  $NH_2$ ;



wherein  $R_4$  is *n*-propyl or  $NHCH_2CH_3$ ;

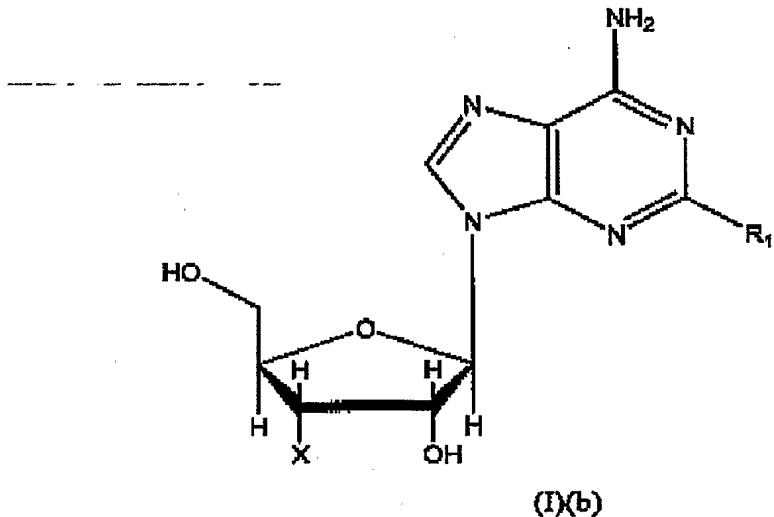
or a pharmaceutically acceptable salt thereof.

Preferred compounds of formula (I) are compounds of formula (I)(a) or (I)(b):



wherein:

when X = OH, R<sub>1</sub> is C<sub>5</sub>-C<sub>6</sub> alkoxy, phenoxy substituted with nitrile, phenyl or 3-isopropyl, (5-indanyl)oxy, C<sub>5</sub> or C<sub>6</sub> alkylamino, (N-methyl, N-isoamylamino), a C<sub>2</sub>sulfone group, or a C<sub>7</sub> alkyl group; or  
 when X = H, R<sub>1</sub> is *n*-hexyloxy;



wherein:

when X = OH, R<sub>1</sub> is phenoxy, substituted phenoxy, C<sub>1</sub> or C<sub>2</sub> alkylamino, phenylamino with either methoxy or fluoro substituents, or OCH<sub>2</sub>CH<sub>2</sub>OH; or  
 when X = H, R<sub>1</sub> is *n*-hexyloxy.

There is also provided according to the invention a compound of the invention for use as a medicament.

It is believed that compounds of formulae (I)-(IV) have analgesic and/or anti-inflammatory activity and can be administered with reduced probability and severity of side effects compared to other adenosine receptor agonists.

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, particularly hyperalgesia.

There is also provided according to the invention a method of preventing, treating, or ameliorating pain (particularly hyperalgesia) which comprises administering a

compound of formula (I), (II), (III), or (IV) to a subject in need of such prevention, treatment, or amelioration.

Preferred compounds of formula (I), (II), (III), and (IV) are detailed in the Examples.

Compounds of formulae (I)-(IV) are believed to be effective in inhibiting pain perception in mammals suffering from pain, in particular neuropathic or inflammatory pain, even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. Therefore, it is believed that compounds of formulae (I)-(IV) can treat pain (particularly neuropathic and inflammatory pain) without causing the significant side effects associated with administration of other adenosine receptor agonists.

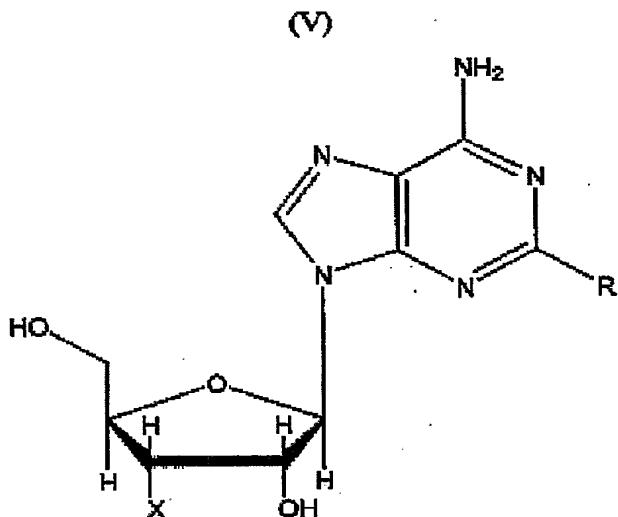
As mentioned above hyperalgesia is a consequence in most instances of tissue damage, either damage directly to a sensory nerve, or damage of the tissue innervated by a given sensory nerve. Consequently, there are many conditions in which pain perception includes a component of hyperalgesia.

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of neuropathy, including Diabetic Neuropathy, Polyneuropathy, Cancer Pain, Fibromyalgia, Myofascial Pain Syndrome, Osteoarthritis, Pancreatic Pain, Pelvic/Perineal pain, Post Herpetic Neuralgia, Rheumatoid Arthritis, Sciatica/Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, HIV pain, Trigeminal Neuralgia, Chronic Neuropathic Pain, Lower Back Pain, Failed Back Surgery pain, back pain, post-operative pain, post physical trauma pain (including gunshot, road traffic accident, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel Pain, Phantom Limb Pain, Obstetric Pain (labour/C-Section), Renal Colic, Acute Herpes Zoster Pain, Acute Pancreatitis Breakthrough Pain (Cancer), Dysmenorrhoea/Endometriosis.

According to the invention there is also provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of inflammatory disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage, including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillain Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis, bowel pain, cancer pain, back pain, fibromyalgia, post-operative pain.

It has also been appreciated that spongiosine may be effective in the prevention, treatment, or amelioration of ischaemic pain. It is believed that compounds related to spongiosine may also be effective against ischaemic pain.

According to the invention there is provided use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, in particular ischaemic pain:



wherein R is C<sub>1-4</sub> alkoxy, and X is H or OH,  
or a pharmaceutically acceptable salt thereof.

Preferably R is C<sub>1-4</sub> alkoxy, and X is OH, or a pharmaceutically acceptable salt thereof.

There is also provided according to the invention a method of preventing, treating, or ameliorating ischaemic pain, which comprises administering a compound of formula (V) to a subject in need of such prevention, treatment, or amelioration.

It has also been appreciated that compounds of formula (I)-(IV) may be effective in the prevention, treatment, or amelioration of ischaemic pain.

The term "ischaemic pain" is used herein to mean pain associated with a reduction in blood supply to a part of the body. A reduced blood supply limits the supply of oxygen (hypoxia) and energy to that part of the body. Ischaemia arises from poor blood perfusion of tissues and so ischaemic pain arises in coronary artery disease, peripheral artery disease, and conditions which are characterized by insufficient blood flow, usually secondary to atherosclerosis. Other vascular disorders can also result in ischaemic pain. These include: left ventricular hypertrophy, coronary artery disease, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart

insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis obliterens), arteritis, diastolic dysfunction and systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (both Types I and II), thromboembolisms. Haemorrhagic accidents can also result in ischaemic pain. In addition poor perfusion can result in neuropathic and inflammatory pain arising from hypoxia-induced nerve cell damage (e.g. in cardiac arrest or bypass operation, diabetes or neonatal distress).

There is further provided according to the invention use of a compound of the invention for the manufacture of a medicament for the prevention, treatment, or amelioration of inflammation.

There is further provided according to the invention a method of prevention, treatment, or amelioration of inflammation, which comprises administering a compound of the invention to a subject in need of such prevention, treatment, or amelioration.

In particular, it is believed that compounds of the invention (i.e. compounds of formula (I), (II), (III), (IV), or (V)) can be used to prevent, treat, or ameliorate inflammation caused by or associated with: cancer (such as leukemias, lymphomas, carcinomas, colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic, lung, breast, and prostate metastases, etc.); auto-immune disease (such as organ transplant rejection, lupus erythematosus, graft v. host rejection, allograft rejections, multiple sclerosis, rheumatoid arthritis, type I diabetes mellitus including the destruction of pancreatic islets leading to diabetes and the inflammatory consequences of diabetes); autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis); cardiovascular conditions associated with poor tissue perfusion and inflammation such as stroke, ischaemia-reperfusion injury, claudication, spinal cord injury, congestive heart failure, vasculitis, haemorrhagic shock, vasospasm following subarachnoid haemorrhage, vasospasm following cerebrovascular accident,

pleuritis, pericarditis, the cardiovascular complications of diabetes; ischaemia-reperfusion injury, ischaemia and associated inflammation, restenosis following angioplasty and inflammatory aneurysms; epilepsy, neurodegeneration (including Alzheimer's Disease), muscle fatigue or muscle cramp (particularly athletes' cramp), arthritis (such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis), fibrosis (for example of the lung, skin and liver), multiple sclerosis, sepsis, septic shock, encephalitis, infectious arthritis, Jarisch-Herxheimer reaction, shingles, toxic shock, cerebral malaria, Lyme's disease, endotoxic shock, gram negative shock, haemorrhagic shock, hepatitis (arising both from tissue damage or viral infection), deep vein thrombosis, gout; conditions associated with breathing difficulties (e.g. chronic obstructive pulmonary disease, impeded and obstructed airways, bronchoconstriction, pulmonary vasoconstriction, impeded respiration, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, bronchial allergy and/or inflammation, asthma, hay fever, rhinitis, vernal conjunctivitis and adult respiratory distress syndrome); conditions associated with inflammation of the skin (including psoriasis, eczema, ulcers, contact dermatitis); conditions associated with inflammation of the bowel (including Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, inflammatory bowel disease); HIV (particularly HIV infection), cerebral malaria, bacterial meningitis, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, osteoporosis and other bone resorption diseases, osteoarthritis, rheumatoid arthritis, infertility from endometriosis, fever and myalgia due to infection, cachexia secondary to cancer, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment, and other conditions mediated by excessive anti-inflammatory cell (including neutrophil, eosinophil, macrophage and T-cell) activity.

Compounds of the invention that are selective agonists of adenosine A<sub>2A</sub> and/or A<sub>3</sub> receptors are particularly preferred because it is believed that such compounds will have strong anti-inflammatory activity. By selective agonists of adenosine A<sub>2A</sub>

and/or A<sub>3</sub> receptors is meant agonists that activate adenosine A<sub>2A</sub> and/or A<sub>3</sub> receptors at concentrations that are lower (preferably one thousandth to one fifth) than required to activate adenosine A<sub>1</sub> receptors. Furthermore, A<sub>1</sub> receptors have pro-inflammatory activity, so such effects are expected to be minimised for compounds that are selective for A<sub>2A</sub> and/or A<sub>3</sub> receptors.

Compounds of the invention are believed to be much more effective at low doses than other adenosine receptor agonists. Thus, it is expected that compounds of the invention can be effectively administered at doses at which they have reduced probability and severity of side effects, or at which side effects are not observed. Such compounds provide significant advantages over the vast majority of other adenosine receptor agonists which only have anti-inflammatory effects at the same concentrations at which serious side effects are observed.

Compounds of the invention may alternatively or additionally have reduced probability and severity of side effects compared to other adenosine receptor agonists.

It has also been appreciated that compounds of formulae (I)-(V) may be effective in preventing, treating, or ameliorating macro and micro vascular complications of type 1 or 2 diabetes (including retinopathy, nephropathy, autonomic neuropathy), or blood vessel damage caused by ischaemia (either diabetic or otherwise) or atherosclerosis (either diabetic or otherwise).

According to the invention, there is provided use of a compound of formula (I), (II), (III), (IV), or (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of macro or micro vascular complications of type 1 or 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis.

According to the invention there is also provided a method of preventing, treating, or ameliorating macro or micro vascular complications of type 1 or 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis, in a subject in need of such prevention, treatment, or

amelioration, which comprises administering a compound of formula (I), (II), (III), (IV), or (V) to the subject.

Preferred compounds of formula (V) are 2-methoxyadenosine, 2-ethoxyadenosine, and 2-butyloxyadenosine.

Compounds of formulae (I)-(V) are believed to be effective in prevention, treatment, or amelioration of ischaemic pain (or macro or micro vascular complications of type 1 and 2 diabetes, including retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis (either diabetic or otherwise)) even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. At these doses, it is believed that the compounds do not cause the significant side effects associated with administration of higher doses of spongosine, or other adenosine receptor agonists.

Compounds of formula (I)-(V) are also believed to be effective in the promotion of wound healing. According to the invention there is provided use of a compound of formula (I), (II), (III), (IV), or (V) in the manufacture of a medicament for the promotion of wound healing. There is also provided according to the invention a method of promoting wound healing in a subject, which comprises administering a compound of formula (I), (II), (III), (IV), or (V) to the subject.

The amount of a compound of formula (I)-(V) that is administered to a subject is preferably an amount which gives rise to a peak plasma concentration that is less than the EC50 value of the compound at adenosine receptors (preferably at pH 7.4).

It will be appreciated that the EC50 value of the compound is likely to be different for different adenosine receptors (i.e. the A1, A2A, A2B, A3 adenosine receptors). The amount of the compound that is to be administered should be calculated relative to the lowest EC50 value of the compound at the different receptors.

Thus, preferably the amount of a compound of the invention that is administered to a subject should be an amount which gives rise to a peak plasma concentration that is less than the lowest EC50 value of the compound at adenosine receptors.

Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value.

Preferably the amount of a compound of the invention that is administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value of the compound at adenosine receptors.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour between one thousandth and one fifth, or one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the EC50 value of the compound at adenosine receptors at pH 7.4.

For the avoidance of doubt, the EC50 value of a compound is defined herein as the concentration of the compound that provokes a receptor response halfway between the baseline receptor response and the maximum receptor response (as determined, for example, using a dose-response curve).

The EC50 value should be determined under standard conditions (balanced salt solutions buffered to pH 7.4). For EC50 determinations using isolated membranes, cells and tissues this would be in buffered salt solution at pH 7.4 (e.g. cell culture medium), for example as in Daly *et al.*, Pharmacol. (1993) 46, 91-100), or preferably

as in Tilburg *et al* (J. Med. Chem. (2002) 45, 91-100). The EC<sub>50</sub> could also be determined *in vivo* by measuring adenosine receptor mediated responses in a normal healthy animal, or even in a tissue perfused under normal conditions (i.e. oxygenated blood, or oxygenated isotonic media, also buffered at pH 7.4) in a normal healthy animal.

Alternatively, the amount of a compound of the invention that is administered may be an amount that results in a peak plasma concentration that is less than the lowest or highest K<sub>d</sub> value of the compound at adenosine receptors (i.e. less than the lowest or highest K<sub>d</sub> value of the compound at A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub> adenosine receptors). Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one third, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest or highest K<sub>d</sub> value.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for at least one hour between one thousandth and one fifth, more preferably between one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the K<sub>d</sub> value of the compound at adenosine receptors.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one fiftieth to one third, or one tenth to one fifth) of the lowest or highest K<sub>d</sub> value of the compound at adenosine receptors.

The K<sub>d</sub> value of the compound at each receptor should be determined under standard conditions using plasma membranes as a source of the adenosine receptors derived

either from tissues or cells endogenously expressing these receptors or from cells transfected with DNA vectors encoding the adenosine receptor genes. Alternatively whole cell preparations using cells expressing adenosine receptors can be used. Labelled ligands (e.g. radiolabelled) selective for the different receptors should be used in buffered (pH7.4) salt solutions (see e.g. Tilburg et al, J. Med. Chem. (2002) 45, 420-429) to determine the binding affinity and thus the Kd of the compound at each receptor.

Alternatively, the amount of a compound of the invention that is administered may be an amount that is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount (or dose) of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount of the compound that gives rise to the side effects.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth of the minimum dose that gives rise to the side effects.

Alternatively, the amount of a compound of the invention that is administered may be an amount that gives rise to plasma concentrations that are one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one

thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that cause bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that causes the side effects.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth, of the minimum plasma concentration that causes the side effects.

It is expected that the amount of a compound of the invention that is administered should be 0.001-15 mg/kg. The amount may be less than 6 mg/kg. The amount may be at least 0.001, 0.01, 0.1, or 0.2 mg/kg. The amount may be less than 0.1, or 0.01 mg/kg. Preferred ranges are 0.001-10, 0.001-5, 0.001-2, 0.001-1, 0.001-0.1, 0.001-0.01, 0.01-15, 0.01-10, 0.01-5, 0.01-2, 0.01-1, 0.1-10, 0.1-5, 0.1-2, 0.1-1, 0.2-15, 0.2-10, 0.2-5, 0.2-2, 0.2-1.2, 0.2-1, 0.6-1.2, mg/kg.

Preferred doses for a human subject (for example a 70kg subject) are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7-70mg, or 14-70mg.

It is believed that the dosage amounts specified above are significantly lower (up to approximately 1000 times lower) than would be expected to be required for an analgesic or an anti-inflammatory effect based on the EC50 value of the compound at the adenosine A<sub>2A</sub> receptor.

The dosage amounts specified above are aimed at producing plasma concentrations that are approximately one thousandth to one hundredth of the EC50 value of spongiosine at the adenosine A1 receptor.

The appropriate dosage of a compound of the invention will vary with the age, sex, weight, and condition of the subject being treated, the potency of the compound, and the route of administration, etc. The appropriate dosage can readily be determined by one skilled in the art.

A compound of the invention may be administered with or without other therapeutic agents, for example analgesics or anti-inflammatories (such as opiates, steroids, NSAIDs, cannabinoids, tachykinin modulators, or bradykinin modulators) or anti-hyperalgesics (such as gabapentin, pregabalin, cannabinoids, sodium or calcium channel modulators, anti-epileptics or anti-depressants).

In general, a compound of the invention may be administered by known means, in any suitable formulation, by any suitable route. A compound of the invention is preferably administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally. Other suitable routes include intravenous, intramuscular, subcutaneous, inhaled, and topical. The amount of drug administered will typically be higher when administered orally than when administered, say, intravenously.

It will be appreciated that a compound of the invention may be administered together with a physiologically acceptable carrier, excipient, or diluent.

Suitable compositions, for example for oral administration, include solid unit dose forms, and those containing liquid, e.g. for injection, such as tablets, capsules, vials and ampoules, in which the active agent is formulated, by known means, with a physiologically acceptable excipient, diluent or carrier. Suitable diluents and carriers are known, and include, for example, lactose and talc, together with appropriate binding agents etc.

A unit dosage of a compound of the invention typically comprises up to 500 mg (for example 1 to 500 mg, or (preferably) 5 to 500 mg) of the active agent. Preferably the active agent is in the form of a pharmaceutical composition comprising the active agent and a physiologically acceptable carrier, excipient, or diluent. The preferred dosage is 0.1 to 2, e.g. 0.5 to 1, typically about 0.2 or 0.6, mg of the active agent per kg of the (human) subject. Preferred amounts of the active agent are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7 to 70mg, or 14 to 70mg. At these levels, it is believed that effective treatment can be achieved substantially without a concomitant fall (for example, no more than 10%) in blood pressure.

Preferably a compound of the invention is administered at a frequency of 2 or 3 times per day.

Compounds of the invention can also serve as a basis for identifying more effective drugs, or drugs that have further reduced side effects.

Use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain, or a method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (I) in accordance with the invention may exclude prevention, treatment, or amelioration of pain resulting from damage caused to organs as a consequence of reperfusion following an ischaemic episode, for example a myocardial infarct, or a stroke.

Use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain in accordance with the invention may exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

A method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (V) in accordance with the invention may

exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

Embodiments of the invention are described in the following examples with reference to the accompanying drawings in which:

Figure 1 shows the effect of spongiosine (0.6 mg/kg p.o.) on A: blood pressure in normal rats; B: heart rate;

Figure 2 shows the change in plasma concentration over time after administration of spongiosine.

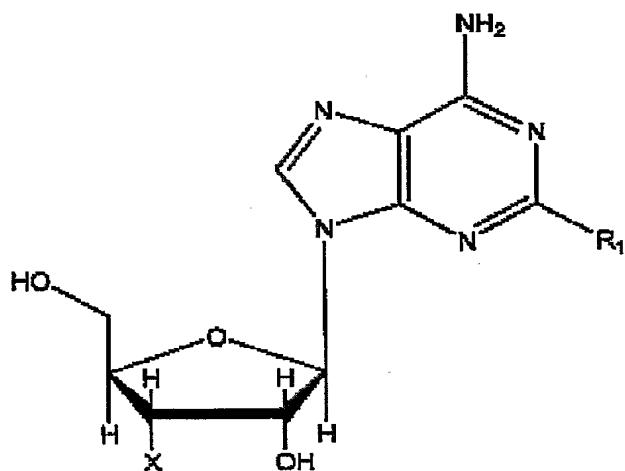
Figure 3 shows the anti-hyperalgesic actions of spongiosine (0.6 mg/kg p.o.) on carrageenan induced hyperalgesia. A: time course (\*p<0.05, \*\*p<0.01 versus vehicle (Sidak's), p>0.05 versus BL over 5 hrs for Spongiosine and IND (Dunnett's)); B: dose dependency of the anti-hyperalgesic effect;

Figure 4 shows the anti-hyperalgesic actions of spongiosine (0.6 mg/kg p.o.) in the chronic constriction injury model of neuropathic pain (\*p<0.05, \*\*p<0.01 vs veh (ANOVA Sidak's);

Figure 5 shows the effect of spongiosine (0.6 mg/kg p.o.) in the presence and absence of naloxone in the chronic constriction injury model of neuropathic pain; and

Figure 6 shows the additive effect of spongiosine and gabapentin in the chronic constriction injury model of neuropathic pain.

Structures of preferred compounds of the invention are given in the Examples below. A Ki value is given for each compound. To calculate this, rat striatal membranes were incubated for 90 minutes at 22°C in the presence of 2nM [<sup>3</sup>H]-CGS21680, 1Unit/mL adenosine deaminase and increasing concentrations of the compound being studied, prior to filtration and liquid scintillation counting.

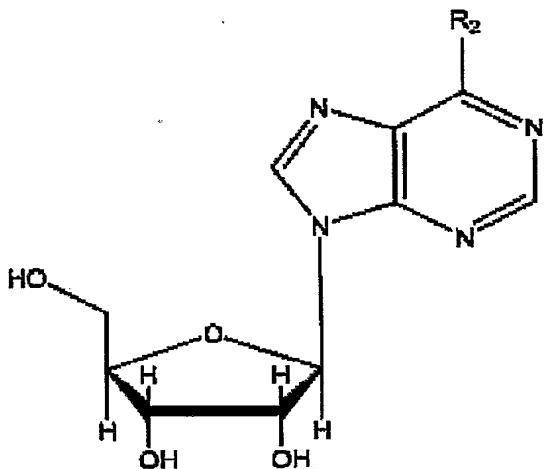
**Example 1****When X = OH**

<b>Compound No.</b>	<b>Structure R<sub>1</sub></b>	<b>(K<sub>i</sub>) nM</b>
1	OCH <sub>3</sub>	1300
2	OCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	280
3	OCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	1500
4	OPh	2500
5	O-(4-cyano)Ph	1300
6	O-(3-Ph)Ph	620
7	5-indanyloxy	760
8	O-(3-CH(CH <sub>3</sub> ) <sub>2</sub> )Ph	560
9	NH(CH <sub>3</sub> )	1356
10	NHCH <sub>2</sub> CH <sub>3</sub>	1200
11	N(CH <sub>3</sub> ) <sub>2</sub>	13350
12	NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	290
13	NHPh	160
14	NH-(4-MeO)Ph	55
15	NH-(4-F)Ph	200
16	NH-cyclopentyl	420
17	NH-cyclohexyl	1000

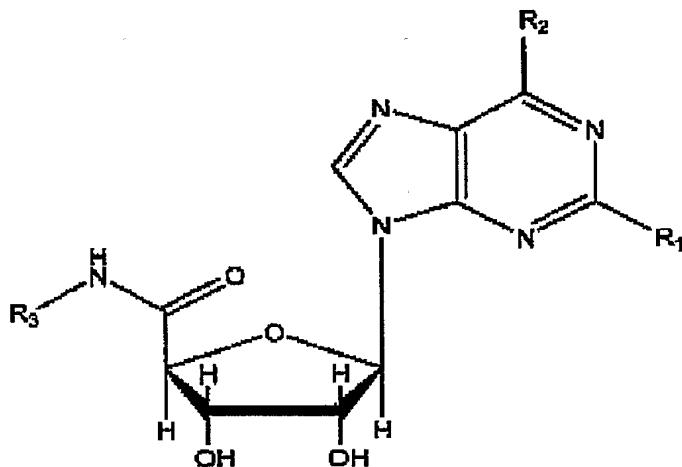
18	N-CH <sub>3</sub> , N-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	4000
19	OCH <sub>2</sub> cyclopentyl	200
20	SO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	39000
21	OCH <sub>2</sub> CH <sub>2</sub> OH	203
22	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	800

When X = H

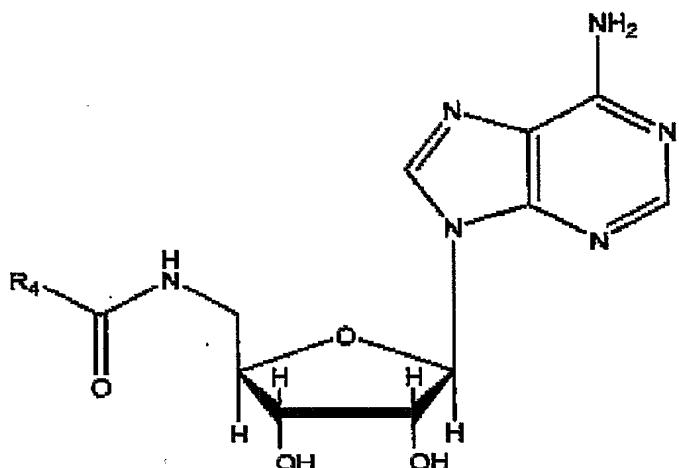
Compound No.	Structure R <sub>1</sub>	(K <sub>i</sub> ) nM
23	O CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	2990

**Example 2**

Compound No.	Structure R <sub>2</sub>	(K <sub>i</sub> ) nM
24	N(CH <sub>3</sub> ) <sub>2</sub>	450000
25	NHCH <sub>2</sub> CHC(CH <sub>3</sub> ) <sub>2</sub>	8600
26	N-CH <sub>3</sub> , N-CH <sub>2</sub> Ph	18500
27	Piperazinyl	5000
28	N-Me, N-(CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> )	13000

**Example 3**

<b>Compound No.</b>	<b>R<sub>1</sub></b>	<b>R<sub>2</sub></b>	<b>R<sub>3</sub></b>	<b>(Ki ) nM</b>
29	H	NH <sub>2</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	1930
30	H	NH <sub>2</sub>	H	270
31	H	NHCH <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	2440
32	OCH <sub>3</sub>	NH <sub>2</sub>	Ph	26100

**Example 4**

Compound No.	Structure R <sub>4</sub>	(Ki ) nM
33	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	16900
34	NHCH <sub>2</sub> CH <sub>3</sub>	6570

**Example 5**

Figure 1: Spongiosine (0.624 mg/kg p.o.) has no significant effect on blood pressure or heart rate. An implantable radiotelemetry device was placed in the abdominal cavity of 6 rats per group. The pressure catheter of the device was inserted in the abdominal aorta and two electrodes tunnelised under the skin in a lead II position (left side of abdominal cavity/right shoulder). Individual rats were placed in their own cage on a radioreceptor (DSI) for data acquisition. A: blood pressure; B: heart rate.

**Example 6**

The EC<sub>50</sub> value of spongiosine at adenosine receptors (measured at pH7.4) is 900ng/ml (3 μM). Figure 2 shows the change in plasma concentration over time after administration of spongiosine at 0.6 mg/kg to a rat. It can be seen that the plasma concentration remains above 2% of the EC<sub>50</sub> value for more than 3 hours. Anti-hyperalgesic effects have been observed (without blood pressure changes) when the

peak plasma concentration is between 1% and 30% of the EC50 value determined in vitro. If the peak plasma concentration reaches the EC50 value profound reductions in blood pressure occur that last for hours.

#### **Example 7**

Figure 3: A. Spongosine (0.624mg/kg p.o.) inhibits carrageenan (CGN) induced thermal hyperalgesia (CITH) with comparable efficacy to indomethacin (3mg/kg, po). B. Concentration-response relationship for Spongosine at 3 hrs post dosing. Carrageenan (2%, 10 microlitres) was administered into the right hind paw. A heat source was placed close to the treated and untreated hind paws, and the difference in the paw withdrawal latencies is shown. Spongosine was administered at the same time as carrageenan.

#### **Example 8**

Figure 4: Spongosine (0.624mg/kg p.o.) inhibits thermal hyperalgesia caused by chronic constriction injury of the rat sciatic nerve. Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed thermal hyperalgesia in the operated leg as judged by the difference in paw withdrawal latencies of the right and left paws. Administration of spongiosine reduced the hyperalgesia as shown by the reduction in the difference between the withdrawal latencies. Spongiosine was as, or more, effective than carbamazepine (CBZ, 100mg/kg s.c.)

#### **Example 9**

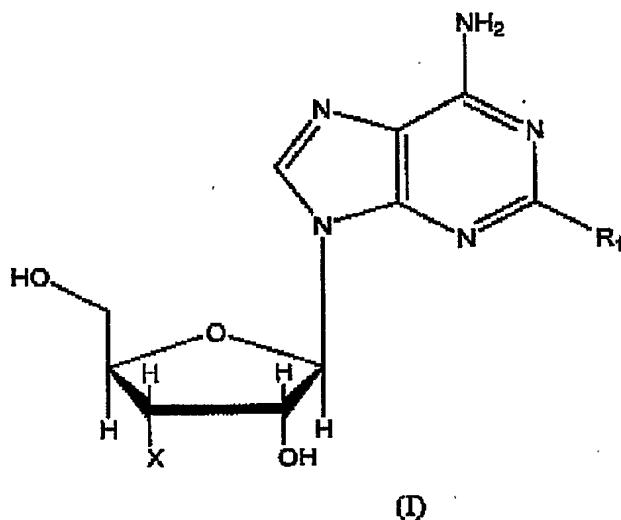
Figure 5: Spongiosine (1.2 mg/kg p.o.) inhibits static allodynia caused by chronic constriction injury of the rat sciatic nerve, both in the presence and absence of naloxone (1 mg/kg s.c.). Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed static allodynia in the operated leg as judged by the difference in paw withdrawal thresholds of the right and left paws. Administration of spongiosine reduced the hyperalgesia as shown by the increased paw withdrawal threshold (PWT) in the presence and absence of naloxone. Veh: vehicle.

**Example 10**

Figure 6: Spongiosine and gabapentin inhibit static allodynia caused by chronic constriction injury of the rat sciatic nerve. Spongiosine and gabapentin were administered (p.o.) in different proportions as indicated in the drawing. The total dose administered is shown on the horizontal axis, and the paw withdrawal threshold (PWT) on the vertical axis. The predicted anti-hyperalgesic effect (derived from the dose response curves obtained with each agent alone) if the effects of the two compounds are additive is shown (•). The observed effects are indicated by (■). It is apparent that the observed effects are not significantly different from those predicted by additivity.

Claims

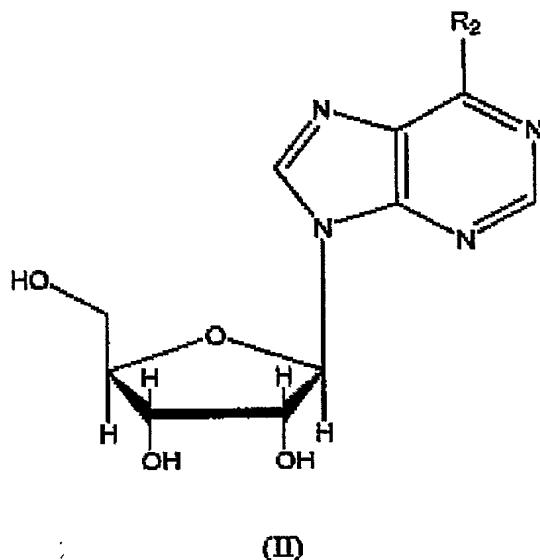
1. A compound of formula (I), (II), (III), or (IV):



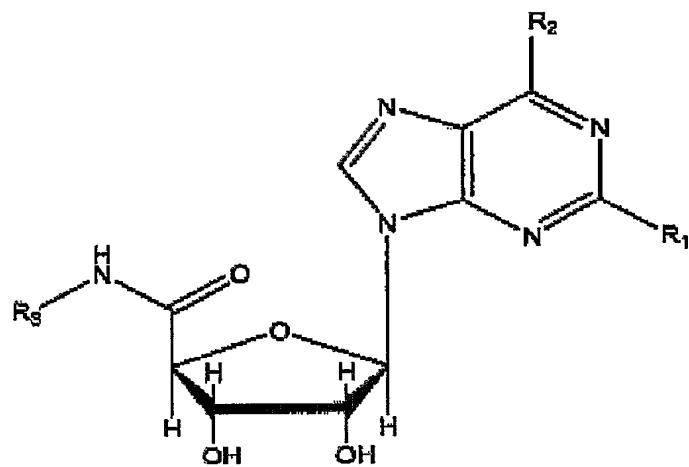
wherein:

when  $X = OH$ ,  $R_1$  is  $C_5$ - $C_6$  alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy,  $C_1$ ,  $C_2$ ,  $C_5$ , or  $C_6$  alkylamino (straight chain or cyclic), phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a  $C_2$  sulfone group, a  $C_7$  alkyl group, or  $OCH_2CH_2OH$ ; or

when  $X = H$ ,  $R_1$  is *n*-hexyloxy;



wherein R<sub>2</sub> is NMe<sub>2</sub>, N-(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));

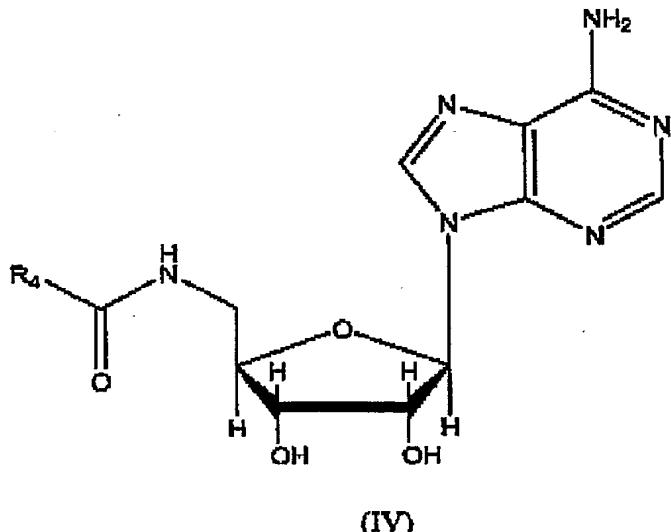


wherein:

when R<sub>1</sub> = H, R<sub>3</sub> is an isopropyl group, and R<sub>2</sub> is either NH<sub>2</sub> or a methylamino group (NHMe); or

when R<sub>1</sub> = H, R<sub>3</sub> is H, and R<sub>2</sub> is NH<sub>2</sub>; or

when R<sub>1</sub> is OMe, R<sub>3</sub> is Ph, and R<sub>2</sub> is NH<sub>2</sub>;



(IV)

wherein  $\text{R}_4$  is *n*-propyl or  $\text{NHCH}_2\text{CH}_3$ ;

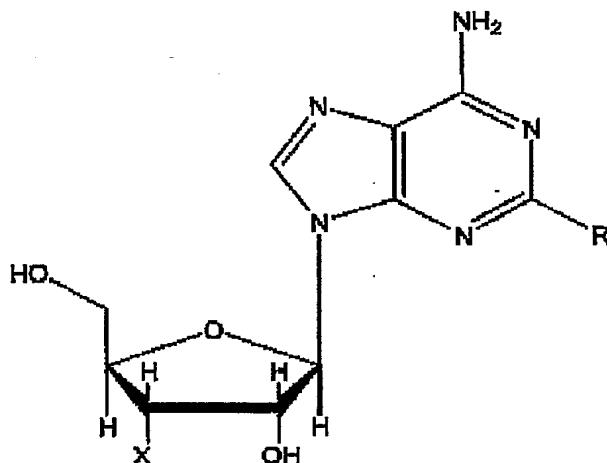
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 with a structure as defined in any of Examples 1-4, excluding compound 13.
3. A compound according to claim 1 or 2 for use as a medicament.
4. Use of a compound according to claim 1 or 2, or compound 13, in the manufacture of a medicament for the prevention, treatment, or amelioration of pain.
5. Use according to claim 4, wherein the pain is hyperalgesia.
6. Use according to claim 5, wherein the hyperalgesia is neuropathic pain.
7. Use according to any of claims 4 to 6 for the prevention, treatment, or amelioration of: pain associated with cancer, pancreatic pain, pelvic/perineal pain, pain associated with HIV infection, chronic neuropathic pain, lower back pain, failed back surgery pain, back pain, post-operative pain, post physical trauma pain, cardiac pain, chest pain, pelvic pain/PID, joint pain, neck pain, bowel pain, phantom limb

pain, obstetric pain, acute herpes zoster pain, acute pancreatitis breakthrough pain, or for the prevention, treatment, or amelioration of neuropathic or other pain caused by, or associated with diabetic neuropathy, polyneuropathy, fibromyalgia, myofascial pain syndrome, osteoarthritis, post herpetic neuralgia, rheumatoid arthritis, sciatica/lumbar radiculopathy, spinal stenosis, temporo-mandibular joint disorder, trigeminal neuralgia, renal colic, dysmenorrhoea/endometriosis.

8. Use according to claim 5, wherein the hyperalgesia is inflammatory pain.
9. Use according to any of claims 4, 5, or 8 wherein the pain is caused by or associated with an inflammatory or immune disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage.
10. Use according to any of claims 4, 5, 8, or 9 for the prevention, treatment, or amelioration of bowel pain, pain associated with cancer, back pain, post-operative pain, or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, autoimmune damage, graft v. host rejection, allograft rejections, fever and myalgia due to infection, fibromyalgia, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis.
11. Use according to claim 4, or use of a compound of formula (V), in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain:

(V)



wherein R is  $C_{1-4}$  alkoxy, and X is H or OH; or a pharmaceutically acceptable salt thereof.

12. Use according to claim 4 or 11 in the manufacture of a medicament for the prevention, treatment, or amelioration of pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis obliterens), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

13. Use of a compound of claim 1 or 2, or a compound of formula (V), in the manufacture of a medicament for the prevention, treatment, or amelioration of macro or micro vascular complications of type 1 and 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis.

14. Use of a compound of claim 1 or 2 for the manufacture of a medicament for the prevention, treatment, or amelioration of inflammation.

15. Use according to claim 14 for the prevention, treatment, or amelioration of inflammation caused by or associated with: cancer (such as leukemias, lymphomas, carcinomas, colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic, lung, breast, and prostate metastases, etc.); auto-immune disease (such as organ transplant rejection, lupus erythematosus, graft v. host rejection, allograft rejections, multiple sclerosis, rheumatoid arthritis, type I diabetes mellitus including the destruction of pancreatic islets leading to diabetes and the inflammatory consequences of diabetes); autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis); cardiovascular conditions associated with poor tissue perfusion and inflammation such as stroke, ischaemia-reperfusion injury, claudication, spinal cord injury, congestive heart failure, vasculitis, haemorrhagic shock, vasospasm following subarachnoid haemorrhage, vasospasm following cerebrovascular accident, pleuritis, pericarditis, the cardiovascular complications of diabetes; ischaemia-reperfusion injury, ischaemia and associated inflammation, restenosis following angioplasty and inflammatory aneurysms; epilepsy, neurodegeneration (including Alzheimer's Disease), muscle fatigue or muscle cramp (particularly athletes' cramp), arthritis (such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis), fibrosis (for example of the lung, skin and liver), multiple sclerosis, sepsis, septic shock, encephalitis, infectious arthritis, Jarisch-Herxheimer reaction, shingles, toxic shock, cerebral malaria, Lyme's disease, endotoxic shock, gram negative shock, haemorrhagic shock, hepatitis (arising both from tissue damage or viral infection), deep vein thrombosis, gout; conditions associated with breathing difficulties (e.g. chronic obstructive pulmonary disease, impeded and obstructed airways, bronchoconstriction, pulmonary vasoconstriction, impeded respiration, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, bronchial allergy and/or inflammation, asthma, hay fever, rhinitis, vernal conjunctivitis and adult respiratory distress syndrome); conditions associated with inflammation of the skin (including psoriasis, eczema, ulcers, contact dermatitis); conditions associated with

inflammation of the bowel (including Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, inflammatory bowel disease); HIV (particularly HIV infection), cerebral malaria, bacterial meningitis, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, osteoporosis and other bone resorption diseases, osteoarthritis, rheumatoid arthritis, infertility from endometriosis, fever and myalgia due to infection, cachexia secondary to cancer, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment, and other conditions mediated by excessive anti-inflammatory cell (including neutrophil, eosinophil, macrophage and T- cell) activity.

16. Use according to any of claims 4 to 15 at a dosage which, after administration to a subject, gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.
17. Use according to any of claims 4 to 16 at a dosage that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.
18. Use according to claim 17, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects.
19. Use according to any of claims 4 to 18 at a dosage which, after administration to a subject, gives rise to a plasma concentration of the compound that is maintained for more than one hour between one thousandth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.
20. Use according to any of claims 4 to 19 at a dosage of less than 6mg/kg.

21. Use according to any of claims 4 to 20 at a dosage of at least 0.01mg/kg.
22. Use according to any of claims 4 to 21 at a dosage of 0.2 to 1mg/kg.
23. A method of preventing, treating, or ameliorating pain which comprises administering a compound according to claim 1 or 2 to a subject in need of such prevention, treatment, or amelioration.
24. A method of preventing, treating, or ameliorating ischaemic pain which comprises administering a compound of formula (V) to a subject in need of such prevention, treatment, or amelioration.
25. A method of prevention, treatment, or amelioration of inflammation, which comprises administering a compound as defined in claim 1 or 2 to a subject in need of such prevention, treatment, or amelioration.
26. A method according to claim 25 for the prevention, treatment, or amelioration of inflammation caused by or associated with: cancer (such as leukemias, lymphomas, carcinomas, colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic, lung, breast, and prostate metastases, etc.); auto-immune disease (such as organ transplant rejection, lupus erythematosus, graft v. host rejection, allograft rejections, multiple sclerosis, rheumatoid arthritis, type I diabetes mellitus including the destruction of pancreatic islets leading to diabetes and the inflammatory consequences of diabetes); autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis); cardiovascular conditions associated with poor tissue perfusion and inflammation such as stroke, ischaemia-reperfusion injury, claudication, spinal cord injury, congestive heart failure, vasculitis, haemorrhagic shock, vasospasm following subarachnoid haemorrhage, vasospasm following cerebrovascular accident, pleuritis, pericarditis, the cardiovascular complications of diabetes; ischaemia-reperfusion injury, ischaemia and associated inflammation, restenosis following angioplasty and inflammatory aneurysms; epilepsy, neurodegeneration (including

Alzheimer's Disease), muscle fatigue or muscle cramp (particularly athletes' cramp), arthritis (such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis), fibrosis (for example of the lung, skin and liver), multiple sclerosis, sepsis, septic shock, encephalitis, infectious arthritis, Jarisch-Herxheimer reaction, shingles, toxic shock, cerebral malaria, Lyme's disease, endotoxic shock, gram negative shock, haemorrhagic shock, hepatitis (arising both from tissue damage or viral infection), deep vein thrombosis, gout; conditions associated with breathing difficulties (e.g. chronic obstructive pulmonary disease, impeded and obstructed airways, bronchoconstriction, pulmonary vasoconstriction, impeded respiration, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, bronchial allergy and/or inflammation, asthma, hay fever, rhinitis, vernal conjunctivitis and adult respiratory distress syndrome); conditions associated with inflammation of the skin (including psoriasis, eczema, ulcers, contact dermatitis); conditions associated with inflammation of the bowel (including Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, inflammatory bowel disease); HIV (particularly HIV infection), cerebral malaria, bacterial meningitis, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, osteoporosis and other bone resorption diseases, osteoarthritis, rheumatoid arthritis, infertility from endometriosis, fever and myalgia due to infection, cachexia secondary to cancer, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment, and other conditions mediated by excessive anti-inflammatory cell (including neutrophil, eosinophil, macrophage and T-cell) activity.

27. A method of preventing, treating, or ameliorating macro or micro vascular complications of type 1 and 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis which comprises administering a compound of claim 1 or 2 , or a compound of formula (V), to a subject in need of such prevention, treatment, or amelioration.

28. A method according to any of claims 23 to 27, wherein the compound is administered at a dose that gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

29. A method according to any of claims 23 to 28, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.

30. A method according to any of claims 23 to 29, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.

31. A method according to any of claims 23 to 30, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.

32. A method according to any of claims 23 to 31, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.

33. A method according to any of claims 23 to 32, wherein the compound is administered to the subject in an amount that is one ten thousandth to one fifth of the minimum amount of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

34. A method according to any of claims 23 to 33, wherein the compound is administered at a dose that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the dose is to be administered.

35. A method according to claim 34, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects

36. A method according to any of claims 23 to 35, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the minimum plasma concentration of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

37. A method according to any of claims 23 to 36, wherein the compound is administered at a dose that results in a plasma concentration of the compound that is maintained for more than one hour between one hundredth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

38. A method according to any of claims 23 to 37, wherein the compound is administered at a dose of less than 6mg/kg.

39. A method according to any of claims 23 to 38, wherein the compound is administered at a dosage of 0.001 to 6 mg/kg.

40. A method according to any of claims 23 to 39, wherein the compound is administered at a dose of at least 0.01mg/kg.

41. A method according to any of claims 23 to 40, wherein the compound is administered at a dose of 0.2 to 1mg/kg.

42. A method according to any of claims 23 to 41, wherein the compound is administered orally, parenterally, sublingually, transdermally, intrathecally, transmucosally, intravenously, intramuscularly, subcutaneously, topically, or by inhaling.

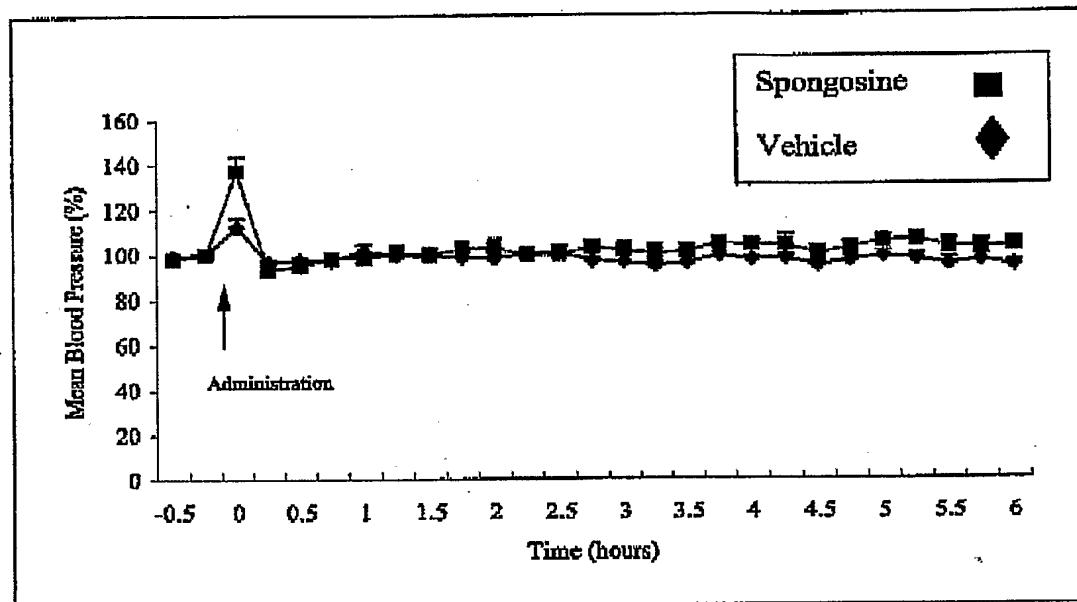
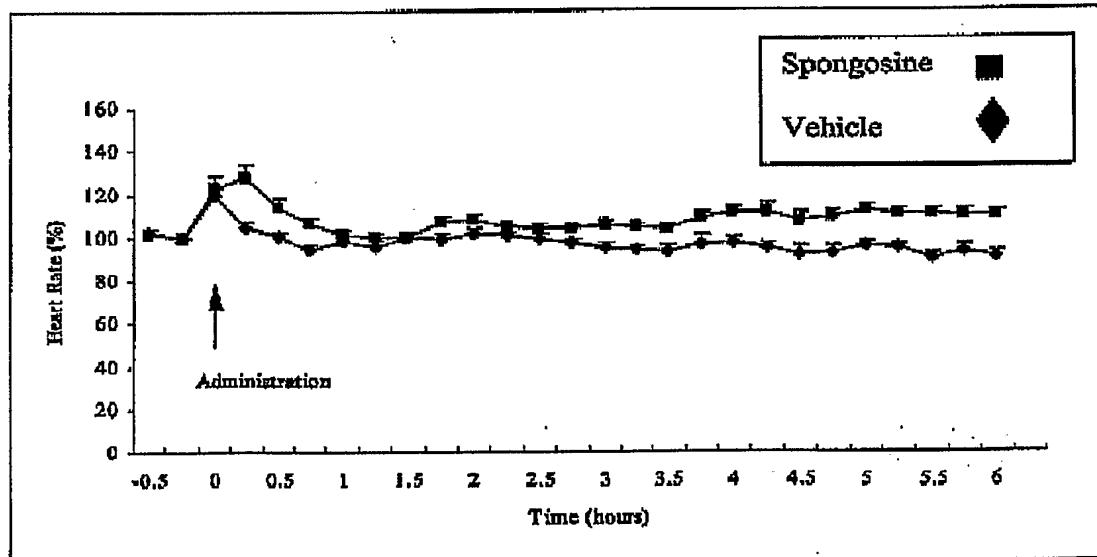
43. A method according to any of claims 23 to 42, wherein the compound is administered at a frequency of 2 or 3-times per day.

44. A method according to any of claims 23 to 43, wherein the subject is a human subject.

45. A method according to any of claims 23 to 44 for the prevention, treatment, or amelioration of ischaemic pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis obliterans), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

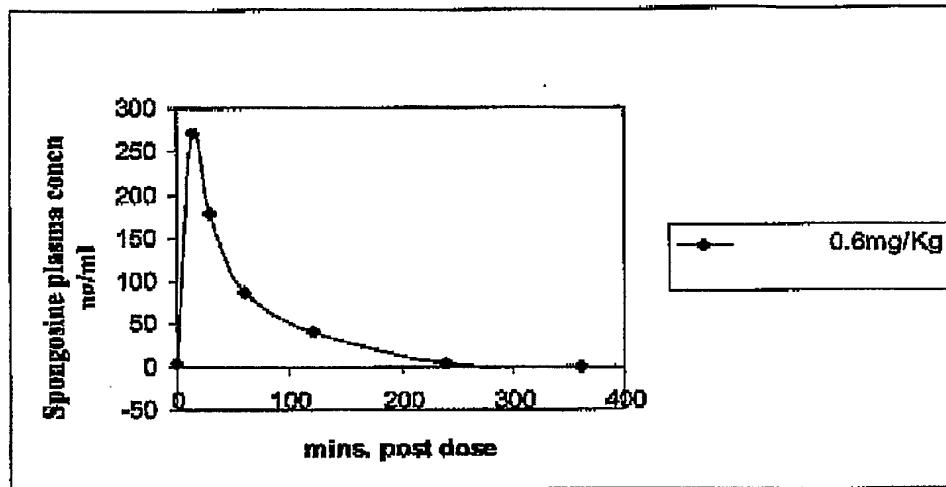
46. A pharmaceutical composition in unit dose form comprising up to 500mg of a compound as defined in claim 1 or 2, and a physiologically acceptable carrier, excipient, or diluent.

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**Figure 1****A)****B)**

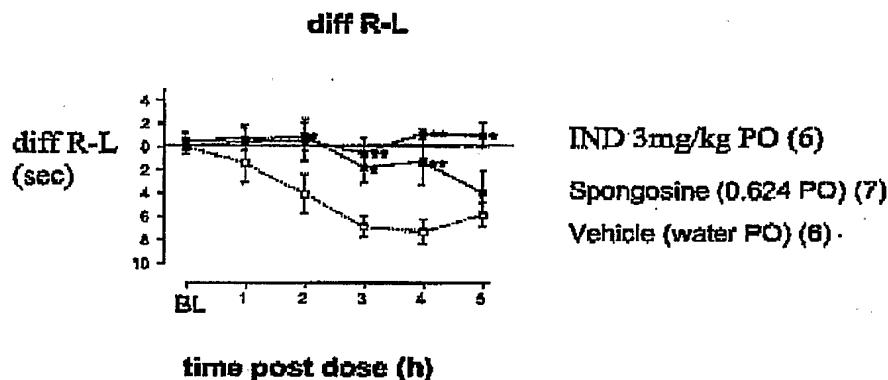
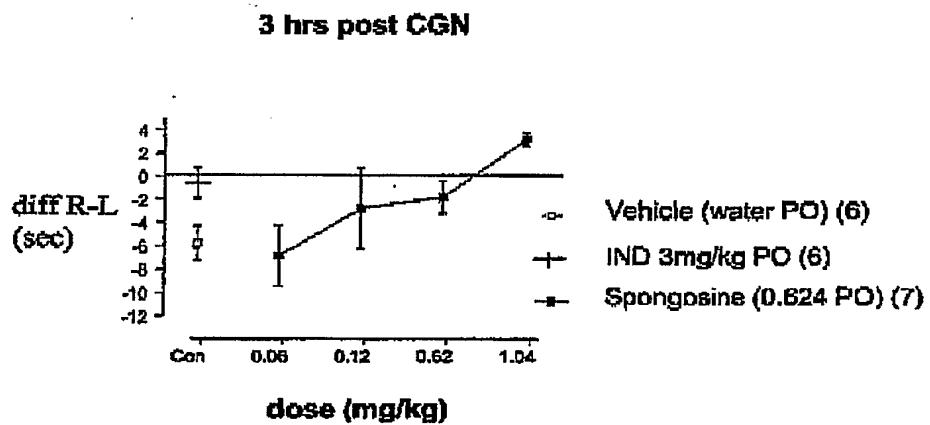


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**Figure 2**

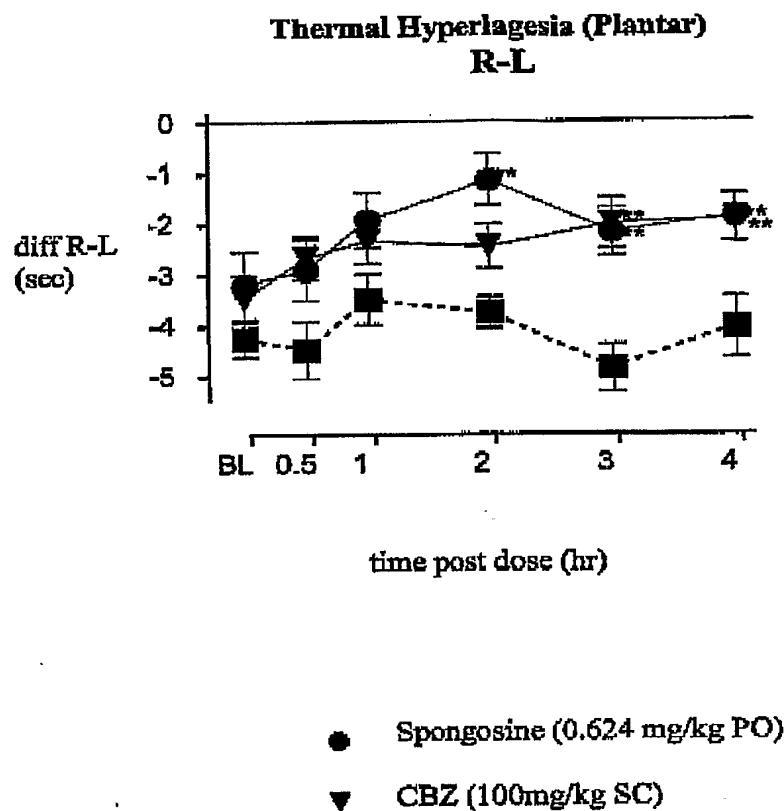


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**Figure 3****A)****B)**

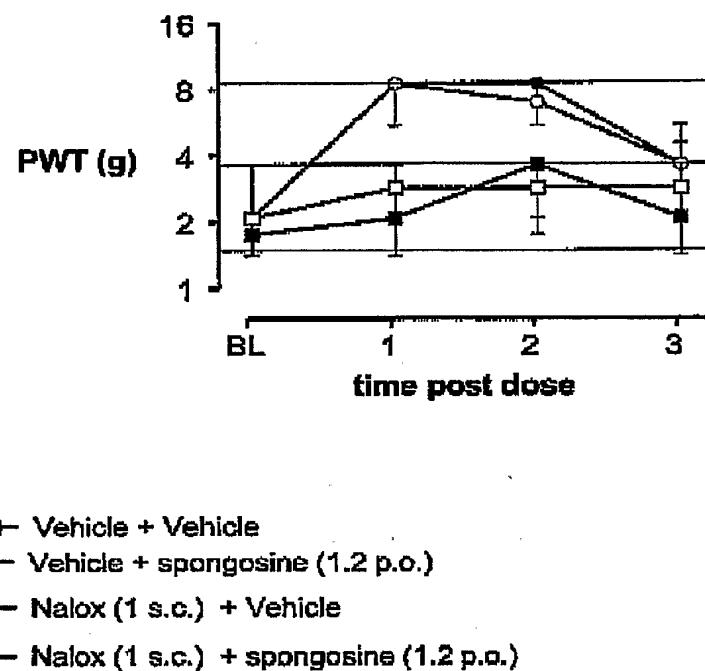


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**Figure 4**



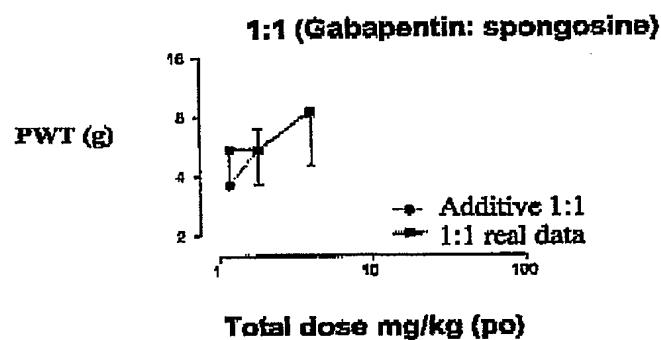
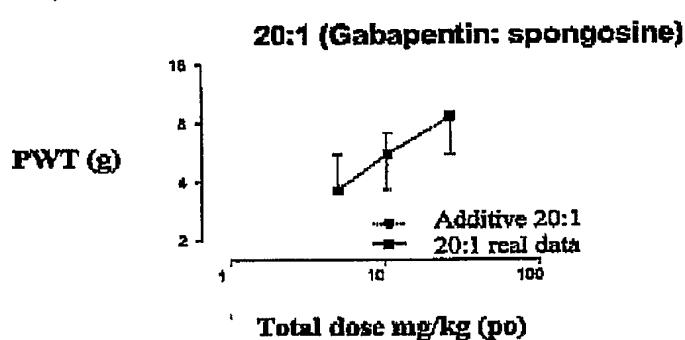
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**Figure 5**



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Figure 6

**A)****B)****C)**